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Polyunsaturated Fatty Acid Metabolism in the Brain and Brain Cells

Corinne Joffre

Abstract

Dietary polyunsaturated fatty acids (PUFAs) have gained more importance these last decades since they regulate the level of long-chain PUFAs (LC-PUFAs) in all cells and especially in brain cells. Because LC-PUFAs, especially those of the n-3 family, display both anti-inflammatory and pro-resolution properties, they play an essential role in neuroinflammation. Neuroinflammation is a hallmark of neurological disorders and requires to be tightly controlled or at least limited otherwise it can have functional consequences and negatively impact the quality of life and well-being of patients. LC-PUFAs exert these beneficial properties in part through the synthesis of specialized pro-resolving mediators (SPMs) that are involved in the resolution of inflammation and to the return of homeostasis. SPMs are promising relevant candidates to resolve brain inflammation and to contribute to neuroprotective functions and lead to novel therapeutics for brain inflammatory diseases. Here we present an overview of the origin and accumulation of PUFAs in the brain and brain cells and their conversion into SPMs that are involved in neuroinflammation and how nutrition induces variations in LC-PUFA and SPM levels in the brain and in brain cells.

Keywords: long-chain polyunsaturated fatty acids (LC-PUFAs), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), specialized pro-resolving mediators (SPMs), nutrition, neuroinflammation, brain, brain cells

1. Introduction

Polyunsaturated fatty acids (PUFA) are essential fatty acids including precursors and long-chain PUFAs (LC-PUFAs). Precursors have to be provided by the diet because they cannot be produced by mammals [1]. They can be converted into LC-PUFAs. However, as the conversion rate is very low in human [2, 3], it is recommended to consume also LC-PUFAs that modulate LC-PUFA composition of brain and brain cells. Altered dietary intake and/or PUFA metabolism has been reported to be involved in a number of neurological disorders *via* sustained neuroinflammatory processes [4]. Indeed, LC-PUFAs are key regulators of inflammation [5]. LC-PUFAs can be metabolized into specific derivatives such as specialized pro-resolving mediators (SPMs) that have anti-inflammatory and pro-resolving properties [6–9], giving the LC-PUFAs and their biological derivatives a growing interest to treat inflammation and more specifically neuroinflammation. Hence, they may

represent a relevant alternative or complementary strategy to treat pathologies involving neuroinflammation. Here, we will review the literature on PUFAs and their bioactive lipid derivatives in the brain and brain cells. The book chapter will be divided in two main sections: in the first one, we will report data on the origin of PUFAs in the brain and on PUFA content in brain and brain cells and in the second one, we will review recent data on the bioactive lipid derivatives and their role in neuroinflammation. We will discuss how nutrition, an environmental factor to which individuals are exposed throughout their life, is a factor of variation of PUFA and their mediator contents in both sections. We will focus on total brain but also on brain cells since brain cells are differently affected by dietary supply.

2. PUFAs in the brain and brain cells

2.1 Origin of PUFAs in the brain

2.1.1 Metabolism of PUFAs

PUFAs are fatty acids containing more than one double bond on their carbon chain. They are classified into two main series, the n-6 PUFAs and the n-3 PUFAs depending on the position of the first double bond from the methyl terminal end. N-6 PUFAs have the first double bond at the 6th carbon and n-3 PUFAs at the 3rd. Of these two series, linoleic acid (LA) and alpha-linolenic acid (ALA) are the precursors and are essential fatty acids because mammals cannot synthesize them. *In vivo*, these precursors can be elongated, desaturated and beta-oxidized into fatty acids with additional double bonds and carbon atoms leading to long-chain PUFAs (LC-PUFAs, ≥ 20 carbon atoms) (**Figure 1**). This metabolic pathway requires specific $\Delta 6$ and $\Delta 5$ desaturases and elongases that are common to both n-6 and n-3 PUFAs, meaning that these pathways are in competition [10]. LC-PUFA

Figure 1. Synthesis pathways of n-6 and n-3 LC-PUFA and main dietary sources of PUFAs. LA: linoleic acid; LNA: linolenic acid; AA: arachidonic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

biosynthesis takes place mainly in the liver, especially in both microsomes and peroxisomes [11]. However, the brain also possesses the enzymatic equipment and can synthesize LC-PUFAs. The main LC-PUFAs for the n-6 and n-3 series, due to their role as precursors of bioactive derivatives and due to their level in the brain, are arachidonic acid (AA, 20:4 n-6) and docosahexaenoic acid (DHA, 22:6 n-3) [12, 13]. Eicosapentaenoic acid (EPA, 20:5 n-3) is also an important n-3 LC-PUFA as it is also a precursor of bioactive derivatives despite its low level in the brain because of its rapid β -oxidation [14]. Docosapentaenoic acid (DPA, 22:5 n-6) for the n-6 family is also relevant because it replaces DHA in the membranes in case of dietary n-3 PUFA deficiency. LC-PUFAs are mainly esterified in phospholipids. They are also present as free LC-PUFA in very low amount: 1 nmole/g tissue *versus* 10 μ moles/g [15].

2.1.2 Dietary origin

The precursors LA and ALA are found mainly in vegetables, oils, and seeds (60% of LA in sunflower oil and 10% of ALA in rapeseed oil, for example) (**Figure 1**) [16, 17]. Although human can synthesize LC-PUFAs from these precursors, the conversion efficiency is very low (<5%) even in healthy adults [2, 3]. Hence, the main part of LC-PUFAs comes from the diet. AA is found in meats (5–10%) and eggs (15%) [18, 19] and DHA and EPA are found in fatty fishes (18.7% EPA + DHA in salmon, 32.9% EPA + DHA in tuna, for example) (**Figure 1**) [20]. However, lean fishes (sole, codfish, etc.) contain also appreciable amounts of DHA and EPA. Therefore, LC-PUFAs dietary intakes are crucial to maintain adequate levels of LC-PUFAs in membranes. That is why there are dietary recommendations for PUFAs. Dietary intakes recommend ~500 mg/day in EPA and DHA (2 portions of fish/week) and a ratio LA/ALA close to 4–5 to meet all the needs of the body into DHA and to protect against cardiovascular disease risk [21, 22]. Preclinical and clinical studies indicate that increasing dietary ALA and reducing LA are beneficial in increasing n-3 LC-PUFA bioavailability [23, 24]. Despite these recommendations, dietary n-3 PUFA intake is insufficient, both for the precursor ALA and the LC-PUFAs DHA and EPA. Indeed, in the western diet, there is an imbalance between n-6 and n-3 PUFAs leading to an n-3 PUFA consumption 12–20 times lower than n-6 PUFA consumption [10, 25]. This is due to the increased industrialization in the developed nations accompanied by changes in dietary habits. It is particularly characterized by an increase in LA and AA together with a decrease in ALA and DHA. A high intake of LA associated with a low intake of ALA leads to the accumulation of n-6 PUFAs, including AA. In case of severe n-3 PUFA deficiency, the expression of desaturases and elongases are upregulated in the liver in order to compensate and provide DHA to the brain [26, 27]. In addition, under dietary n-3 PUFA deficiency, the half-life of brain DHA is increased by twofold as under balanced diet [28]. Dietary lipids, representing 35–40% of total energy intake, are essentially found (90–95%) in the form of triglycerides (a glycerol backbone with three fatty acids). They are also found in the form of phospholipids (in which the 3-position on the glycerol is replaced by a phosphorylated alcohol function). There is still a debate concerning the better form to enhance EPA/DHA bioavailability, krill oil as a source of phospholipids or fish oil as a source of triglycerides [29, 30]. More studies have to be performed.

2.2 PUFA content in the brain

The brain contains high levels of PUFAs (25–30%) that are mainly DHA (n-3 PUFA) (12–14% of total fatty acids) and AA (n-6 PUFA) (8–10% of total fatty acids) [12, 31–35]. Most LC-PUFAs accumulate during brain development, especially

during the perinatal period: in humans between the beginning of the third trimester of gestation and 2 years and in rodents between the 7th and the 21st postnatal day [36–38]. These periods correspond to the rapid neuronal maturation, synaptogenesis, and gray matter expansion [39, 40]. The brain LC-PUFA content differs in brain structures [12, 31, 35, 41, 42], for example, in the adult C57Bl6/J mice, AA is higher in hippocampus (10.2%), followed by the prefrontal cortex (9.7%), the hypothalamus (8.5%), the cortex (7.7%), the cerebellum (6.5%), and the brain stem (5.5%) [12]. DHA is higher in the prefrontal cortex (14.3%) and in the hippocampus (13.7%), followed by cerebellum (12.2%) and cortex (11.9%), hypothalamus (10.1%), and brain stem (8.2%) [12]. Then the AA/DHA ratio varies from 0.75 to 0.85 in the hypothalamus and hippocampus to 0.54 in the cerebellum. These variations may be due to different LC-PUFA entry mechanisms into the brain or to different incorporation into membranes of cells composing the structure considered. These levels are comparable in human: prefrontal cortex contains between 12.3 and 15.9% of DHA in rats and mice and between 14.1 and 15.9% [12, 35, 43, 44].

2.3 PUFA content in brain cells

Brain cells comprise neurons and glial cells: 70% astrocytes, 10–15% oligodendrocytes, and 10–15% microglial cells [45]. Very few studies reported the fatty acid composition of the individual cells. Bourre et al. determined the fatty acid composition in neurons, astrocytes, and oligodendrocytes in 15- or 60-days rats and confirmed previous results obtained in 1973 and 1981 [46–49]. We recently described the fatty acid composition of microglial cells in 21-days mice [46, 50].

Neurons cannot synthesize LC-PUFAs but can incorporate them in their membranes. They contain 8.2–8.3% DHA and 2.2–2.8% n-3 DPA (22:5 n-3) for n-3 LC-PUFAs, 10.3–15.1% AA, 2.2% n-6 DPA, and 1.0–2.1% adrenic acid (22:4 n-6) for n-6 LC-PUFAs [46]. They contain 3.1–6.9% LA. Then the ratio n-3/n-6 is 0.46–0.50.

Astrocytes are supportive glial cells that play many roles including synaptic transmission and energy metabolite furniture to different neural elements. They respond to all forms of central nervous system (CNS) insults through a process referred to as reactive astrogliosis. Dysfunctions of astrocytes result in pathological changes in the CNS. Astrocytes contain 10.6–12.1% DHA and 0.7–1.3% of n-3 DPA for n-3 LC-PUFAs and 10.1–10.3% of AA, 2.5–2.7% of n-6 DPA and 2.4–2.7% adrenic acid (22:4 n-6) [46]. They contain few PUFA precursors: only 1.2–1.4% of LA and no ALA. The ratio n-3/n-6 is 0.72–0.76.

Oligodendrocytes provide a supporting role for neurons and are involved in the formation of myelin sheaths of nerve cell axons. They are highly dynamic and can respond to environmental influences and neuronal activity. They can also regenerate myelin spontaneously after CNS injury. Any disturbances in their functioning are associated with major diseases of the nervous system. They contain mainly 5.1% DHA for n-3 LC-PUFAs and 9.3% AA and 3.5% n-6 DPA for n-6 LC-PUFAs [46]. They contain not as much as LA: only 2.7%. The ratio n-3/n-6 is 0.33.

Microglial cells are the innate immune cells of the brain. They play a major role in synaptogenesis, synapse structure and function, and neuroinflammation. They perpetually scan and control their environment and once activated, they deliver pro-inflammatory and pro-regeneration responses. Their fatty acid composition differs from that of the other brain cells. In all these cells, DHA is the main fatty acid. Microglial cells are characterized by few DHA (<1%) and n-3 DPA (0.1%) but high content of EPA (3.7%) [50]. They contain few AA (1.6%). They contain PUFA precursors: 8.0% LA and 1.3% ALA. The ratio n-3/n-6 is 0.42. This microglial fatty acid composition also differs from the whole brain hippocampus that contains higher DHA than EPA [51]. Then, it seems that EPA metabolism is different in microglial cells than in other brain cells and the

whole brain structure. It is not highly β -oxidized as in the whole brain [52]. More studies have to be performed to elucidate the role of EPA in microglial cells.

2.4 Nutrition as a major factor of variation of brain and brain cell PUFA content

Nutrition is an environmental factor to which individuals are continuously exposed throughout life. And it is an environmental factor that changed a lot these last decades. Indeed, there was a dramatic reduction in the dietary supply of n-3 PUFAs in western societies associated with a drastic increase in the n-6 PUFAs, leading to an imbalanced n-6/n-3 PUFA ratio estimated at 12–20 in developed countries instead of five recommended [10].

This is particularly important considering that brain fatty acid composition varies with the fatty acids of the dietary supply [53]. Indeed, PUFA content is strongly impacted by the dietary PUFAs in all brain structures [12, 54]. A diet deficient in n-3 PUFA precursor during development and/or adulthood decreases brain DHA in all brain structures; the prefrontal cortex and the hippocampus that contain the highest DHA content are the most sensitive whereas the hypothalamus that contains the lowest DHA, is the least sensitive [12, 31, 55–58]. These differences may be attributed to the evolution of brain performance [59, 60]. In such case of n-3 PUFA deficiency, changes in metabolism occur: the half-life of DHA increases in the brain to reduce its loss [61] and the activity of DHA synthesis enzymes ($\Delta 6$ desaturase and elongase) is increased in the liver [26, 62, 63]. In contrast to the deficiency, the supplementation in n-3 LC-PUFAs increases brain DHA [64–67]. DHA supplementation is more efficient than ALA supplementation to increase brain DHA [68, 69]. A DHA supplementation is also efficient to reverse brain DHA decrease due to an n-3 PUFA deficiency or to aging [33, 70–72]. Also, genetic models of n-3 PUFA enrichment such as Fat-1 mice possess higher brain DHA content [12, 73–77].

Brain cells are also impacted by dietary PUFA supply. An n-3 PUFA precursor-deficient diet decreases DHA in neurons (4.6% *versus* 8.2% in 15-day old animals and 2.4 *versus* 8.3% in 60-day old animals), astrocytes (3.1 *versus* 10.6% in 15-day old animals and 5.7 *versus* 12.1% in 60-day old animals), and oligodendrocytes (0.1% *versus* 5.1% in 60-day old animals) [46]. These changes decrease the n-3/n-6 ratio (0.24 *versus* 0.46–0.50 in neurons, 0.12–0.25 *versus* 0.72–0.76 in astrocytes and 0.02 *versus* 0.33 in oligodendrocytes). Interestingly, we recently find that a maternal n-3 PUFA precursor deficiency increases n-6 DPA but does not affect DHA level in microglial cells in 21-day-old animals, suggesting that these cells are protected from n-3 PUFA deficiency [50]. However, we also report that a maternal n-3 LC-PUFA supplementation increases DHA levels and decreases n-6 DPA levels in these animals, confirming results previously obtained in glial cells [78, 79].

All these results suggest that brain DHA levels are highly variables, depending on the brain structures or brain cells considered and on the dietary fatty acid intake. This may have consequences on inflammatory processes since n-3 LC-PUFAs have immunomodulatory properties [80].

3. Bioactive PUFA derivatives

3.1 Bioactive PUFA derivative metabolism

3.1.1 PUFA derivative synthesis pathways

Some of the immunomodulatory properties of LC-PUFAs are attributed to the synthesis of bioactive lipid mediators. Different lipid mediators are synthesized: those

involved in the regulation of inflammation such as the eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and those implicated in the resolution of inflammation called specialized pro-resolving mediators (SPMs, resolvins, protectins, and maresins) (**Figure 2**). Among the eicosanoids, those synthesized from n-3 PUFAs are less potent inflammatory than those synthesized from n-6 PUFAs [81] highlighting the interest to increase n-3 PUFA and decrease n-6 PUFA contents in the membranes. Then, when co-present, EPA-derived eicosanoids antagonize those synthesized from AA. The main EPA-derived mediators include 3-series prostaglandin (PG), 5-series leukotriene (LT), and 3-series thromboxane (TX), reported to be nonactive (**Figure 2**). DHA is also converted into 3-series PG (**Figure 2**). In addition, eicosanoids synthesized from AA and EPA act in competition as they share the same G-protein-coupled receptors. Moreover, EPA is a competitive inhibitor to AA. Indeed, it reduces the production of AA by inhibiting the activity of $\Delta 5$ desaturase converting dihomo-gamma-linolenic acid (dGLA) into AA [81]. EPA also reduces *in vitro* the production of AA-derived eicosanoids by inhibiting the activity of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) generating the eicosanoids [82–84]. Eicosanoids are synthesized first in the time course of the inflammatory response. Then, there is a switch in the bioactive lipid mediator class: SPMs derived from n-3 LC-PUFAs are synthesized to induce the resolution of inflammation and a return to homeostasis (**Figure 3**). DHA is the precursor of D-series resolvins, neuroprotectin D1 (NPD1), and Maresin 1–2 (Mar1–2) and EPA is the precursor of E-series resolvins, all these derivatives underlying most of the beneficial effects attributed to their precursors [1, 85–87]. These derivatives have both anti-inflammatory and pro-resolution properties without immune suppression [6, 8, 88, 89]. SPMs actively orchestrate and finely tune the inflammatory response. They decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines and accelerate the phagocytosis of cellular debris and dead cells without immune suppression. They are synthesized *via* COX-2, LOX, and cytochrome P450 monooxygenases (CYP450) once they have been released from membrane phospholipids by phospholipase A2 in response to stimulation. These

Figure 2. Main bioactive lipid mediators synthesized from n-3 PUFAs. DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LNA: linolenic acid; LT: leukotriene; NPD1: neuroprotection D1; PG: prostaglandin; SPMs: specialized pro-resolving mediators; Tx: thromboxane.

enzymes are expressed in the brain [90–92]. In response to lipopolysaccharide (LPS) that induces inflammation, COX-2 is rapidly expressed in the hippocampus [69, 93] and inhibition of COX-2 delays resolution of acute inflammation [94]. 15-LOX and 5-LOX are the most abundant LOX in the brain [90]. 15-LOX has a dual role since it is involved in neurodegeneration and neurotoxicity due to the increased stress it generates [95–97] and is also involved in neuroprotection [98]. 15-LOX deletion or inhibition decreases SPM production in the brain and cognitive alterations [90]. CYP450 generates n-6 derived epoxides that are anti-inflammatory [99–102]. These enzymes are also expressed in microglia, astrocytes, oligodendrocytes, and neurons [103–106].

3.1.2 Bioactive lipid mediators

DHA is converted into monohydroxy DHA (17-HDHA) by acetylated COX-2, CYP450, and 15-LOX [107, 108] and then into RvD1 by 5-LOX [109, 110]. RvD1 and its precursors have mostly been described at the periphery but have also been detected in the brain. RvD1 was measured in mouse brain following cerebral ischemia. Its level is increased following a DHA intravenous injection [111] and modulated during inflammation: it decreases at the beginning and then increases during the resolution phase [112]. RvD1 acts through the regulation of micro-RNAs (miRNAs) that modulate the expression of target genes such as inflammatory genes [113–117]. DHA can also be converted into di-hydroxy-DHA termed protectin D1 (PD1) or neuroprotectin D1 (NPD1) when produced in the CNS by 5- and 15-LOX [118–121]. NPD1 was measured in hippocampus. Its level greatly is increased following brain ischemia or acute central LPS injection [70, 122] and decreased in the hippocampus of Alzheimer's disease patients [123]. NPD1 acts through NFκB and then decreases pro-inflammatory gene expression [122, 124, 125]. At last, DHA can also be converted into 14-HDHA and then in Mar1–2 by 12/15-LOX [107, 108, 126]. Mar1 and its precursor 14-HDHA have recently been identified in the hippocampus of mice [70]. Its level is decreased in post-mortem Alzheimer's disease patients contributing to the progression of this pathology [127]. Mar1 promotes the resolution of inflammation, reducing pro-inflammatory cytokines, silencing pro-inflammatory signaling cascades, and enhancing M2 repair macrophage phenotype after cerebral ischemia or spinal cord injury [128–130] (**Figure 3**).

EPA is converted into resolvins E1, E2, and E3 by acetylated COX-2 or CYP450 *via* 18R-HEPE by 5- or 15-LOX [107, 131, 132]. RvE1 and its precursor have been detected in hippocampus [70, 133, 134]. RvE1 inhibits NFκB signaling pathway and then decreases LPS-induced proinflammatory cytokines (TNF-α, IL-6, and IL-1β) gene expression in microglial cells [117].

3.1.3 SPM receptors

SPMs act through specific receptors, some but not all of them have recently been identified. RvD1 acts through lipoxin A4 receptor/formyl peptide receptor 2 (ALX/Fpr2) in rodents and G protein coupling receptor 32 (GPR32) in human [109] at picomolar range but induces biological effects at nanomolar range [110, 135]. RvE1 directly binds to its receptor G protein coupling receptor ChemR23 or chemokine like receptor 1 (CMKLR1) [131]. It is also a partial agonist of a leukotriene B4 receptor (BLT1) [136]. In the CNS, ALX/Fpr2 has been identified in the brainstem, spinal cord, hypothalamus, cortex, hippocampus, cerebellum, and striatum [137] and ChemR23 in the prefrontal cortex, hippocampus, and brainstem [138]. At the cellular levels, these two receptors have been detected in microglial cells [117, 139], neurons [137, 140] and astrocytes [96, 113] (**Figure 3**).

Figure 3. Specialized pro-resolving mediator (SPM) synthesis. 14-HDHA: 14-hydroxy-docosahexaenoic acid; 17-HDHA: 17-hydroxy-docosahexaenoic acid; 18-HEPE: 18-hydroxy-eicosapentaenoic acid; ALX/Fpr2: N-formyl peptide receptor 2; BLT1: leukotriene B₄ receptor; COX-2: cyclooxygenases; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; GPR32/37: G protein-coupled receptor 32/37; LC-PUFAs: long chain polyunsaturated fatty acids; LOX: lipoxygenases.

Other receptors have not been identified yet (Mar1 receptor) [127] or identified only at the periphery in macrophages but not in microglia (NPD1 receptor) [141]. In the next sections, we will focus on the role of these SPMs to better understand the beneficial effects of the n-3 PUFAs.

3.2 Role of bioactive lipid derivatives in neuroinflammation

SPMs have multiple biological roles, focusing to the return to homeostasis. In human serum, DHA- and EPA-derivatives represent 30.7 and 25.9% of the identified SPMs, respectively [142, 143]. The most SPMs studied are RvD1 and RvE1 because they have powerful anti-inflammatory and pro-resolution properties. We will then detail the biological roles for these two bioactive mediators.

3.2.1 Biological role of RvD1 and RvE1 in humans

The effect of RvD1 was mainly studied in patients suffering from Alzheimer's disease. Interestingly, RvD1 levels in cerebrospinal fluid are positively correlated with the enhancement of cognitive functions of patients with dementia [96]. Moreover, it was suggested *in vitro* in macrophages isolated from Alzheimer's patients that RvD1 may be involved in A β phagocytosis [144, 145]. Then the decrease in RvD1 levels in Alzheimer's patient brain could contribute to the disease development. To our knowledge, the effect of RvE1 in humans was shown at the periphery (on patients undergoing hepatobiliary resection, pulmonary

inflammation, and bone disease periodontitis) [146–148] but not at the brain level on patients suffering from neurodegenerative diseases.

3.2.2 Biological roles of RvD1 and RvE1 in rodents

RvD1 and RvE1 are active in reducing the pro-inflammatory status in the CNS. Indeed, the precursors of RvD1, 17R-HDHA, and 17S-HDHA decrease the production of pro-inflammatory cytokines TNF- α in the spinal cord and IL-1 β and TNF- α in the hippocampus [70, 149]. Moreover, RvD1 is able to induce the polarization of macrophages and microglia toward an M2 phagocytic phenotype [150–152]. In addition, RvD1 reduces neuroinflammation *via* miRNA in a model of remote damage [113]. RvE1 also modulates inflammation by reducing the proinflammatory cytokines IL-1 β and IL-6 in the prefrontal cortex and decreases the measures of A β pathology in a murine model of Alzheimer's disease [153]. Furthermore, RvE1 treatment decreases brain microglial activation following traumatic brain injury or peripheral brain injury, decreasing the proportion of activated microglia at the expense of ramified microglia [154, 155].

RvD1 is also involved in the prevention of cognitive deficits. In a systemic inflammation model, cognitive decline is prevented by an intraperitoneal (ip) injection of the precursor of RvD1, 17R-HDHA, and is associated with the restoration of transmission and synaptic plasticity and to the prevention of astrogliosis [154, 156]. Moreover, in a model of traumatic brain injury, cognitive deficits are also prevented by an ip chronic administration of 17R-HDHA [154]. Of note, Fat-1 mice that have more brain n-3 LC-PUFAs have higher hippocampus RvD1 that is associated with less cognitive deficits, a better neuronal survival, a decrease in astrocyte and microglial activation and a reduction in pro-inflammatory status following brain ischemia [77, 157]. Inversely, an inhibition of 15-LOX associated with a decrease in RvD1 induces alterations in synaptic plasticity and working memory [90].

Additionally, RvD and E are also associated with the prevention of depressive-like behaviors [158]. An intracerebroventricular (icv) injection of RvD1, D2, E1, E2, or E3 significantly decreases LPS-induced depressive-like behaviors [159–161]. Moreover, an intrathecal injection of 17R-HDHA prevents the occurrence of depressive-like behaviors and is associated with the decrease of pain perception and a restoration of dopamine and glutamate levels in the brain [149, 162]. RvD1 and D2 have also positive effects in chronic mild stress-induced depression and in post-myocardial infarct depression [163, 164].

3.2.3 Biological roles of RvD1 and RvE1 in in vitro brain cell models

The effects of RvD1 were tested on different brain cells. In microglial cells, RvD1 potentiates the activation of the anti-inflammatory M2 phenotype of microglia, enhancing the effect of the anti-inflammatory cytokine IL-4, Arg1, and Ym1 expression and decreasing CD11b expression [152, 155, 165]. Moreover, we showed that RvD1 decreases LPS-induced proinflammatory cytokine (TNF- α , IL-6 and IL-1 β) gene expression in microglial BV2 cells *via* the modulation of miRNAs [117]. RvD2 inhibits LPS-induced activation of toll-like receptor 4 (TLR4, the receptor of LPS) and its downstream signaling pathway NF κ B [166]. RvE1 plays also a direct role in microglial cells by inhibiting microglial activation and pro-inflammatory cytokine release [117, 155]. These results suggest the pro-resolution activity of RvD1 and RvE1 in microglia. In astrocytes, RvD1 decreases TNF- α release induced by LPS injection [149]. In neurons from spinal nodes, RvD1 increases neurite outgrowth [167].

All these studies point out the central role of n-3 LC-PUFA and their bioactive mediators in the regulation of inflammation in the brain, especially through their effect on microglia.

3.3 Nutrition as a factor of variation of SPM levels

The level of these lipid derivatives is modulated by the diet. Indeed, we recently show that a dietary n-3 LC-PUFA supplementation induces an n-3 LC-PUFA enrichment in the hippocampus associated with an increase in n-3 PUFA-derived SPMs and a decrease in n-6 PUFA-derived SPMs [69]. Our results confirm previous ones reporting that oral administration of EPA and DHA results in the generation of EPA- and DHA-derived mediators in the cortex of aged rats [168] and in the down-regulation of the production of n-6 PUFA-derived mediators [169, 170]. The cellular origin of these bioactive lipid derivatives is still unknown. As described in the paragraph above, we know that dietary PUFA supplementation affects PUFA composition in brain cells that potentially could impact brain cell PUFA lipid derivatives. In response to LPS, n-3 LC-PUFA-supplemented mice display an anti-inflammatory SPM profile whereas n-3 LC-PUFA-deficient mice exhibit a pro-inflammatory SPM profile [69]. These results corroborate previous ones *in vivo* [171–176] and *in vitro* in macrophages [177, 178] and microglia [179–181].

The level of SPMs is also dependent on the regulation of their biosynthesis enzymes. 15-LOX mRNA expression increases in n-3 LC-PUFA supplemented group and decreases in n-3 LC-PUFA deficient diet [27, 69, 182]. 15-LOX has beneficial properties such as neuroprotective properties *via* PPAR- γ activation [98] and preservation of cognitive performance through RvD1 formation [90]. 15-LOX has also detrimental effects as it is implicated in neurodegeneration and neurotoxicity through increase of oxidative stress [95–97].

Changes in SPM level and composition induced by the diet can have a great influence on the pro- and anti-inflammatory status of hippocampus and brain cells and reinforce the recommendation of n-3 PUFA-rich diet.

4. Conclusion

These data highlight that n-3 LC-PUFA and their bioactive lipid derivatives are important regulators of neuroinflammation. SPMs are promising therapeutic compounds: they are of natural origin and act in physiologic dose ranges (nanomolar) as compared to EPA and DHA that act at micromolar ranges, and this confers the main advantage to use SPMs. Both brain n-3 LC-PUFA and SPMs are modulated by the diet in the brain and in brain cells confirming the notable role of nutrition in the regulation of inflammation. Alteration in dietary n-3 PUFAs should have dramatic consequences in brain and brain cell PUFA metabolism and finally in the response to neuroinflammation. The use of SPMs to treat neuroinflammation is still in emergence since some data are missing such as the affinity and function of SPM receptors. This field has to be completed. The instability of SPMs may be bypassed by the use of SPM analogues or by their encapsulation. The clinical form and the way of administration should also be defined.

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References

- [1] Bazinet RP, Layé S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nature Reviews. Neuroscience*. Dec. 2014;**15**(12):771-785
- [2] Kidd PM. Omega-3 DHA and EPA for cognition, behavior, and mood: Clinical findings and structural-functional synergies with cell membrane phospholipids. *Alternative Medicine Review*. Sep. 2007;**12**(3):207-227
- [3] Plourde M, Cunnane SC. Extremely limited synthesis of long chain polyunsaturates in adults: Implications for their dietary essentiality and use as supplements. *Applied Physiology, Nutrition, and Metabolism*. Aug. 2007;**32**(4):619-634
- [4] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews. Neuroscience*. Jan. 2008;**9**(1):46-56
- [5] Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochimica et Biophysica Acta*. Apr. 2015;**1851**(4):469-484
- [6] Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. *The Journal of Experimental Medicine*. Oct. 2000;**192**(8):1197-1204
- [7] Serhan CN. The resolution of inflammation: The devil in the flask and in the details. *The FASEB Journal*. May 2011;**25**(5):1441-1448
- [8] Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. Jun. 2014;**510**(7503):92-101
- [9] Spite M, Serhan CN. Novel lipid mediators promote resolution of acute inflammation: Impact of aspirin and statins. *Circulation Research*. Nov. 2010;**107**(10):1170-1184
- [10] Simopoulos AP. Evolutionary aspects of diet: The omega-6/omega-3 ratio and the brain. *Molecular Neurobiology*. Oct. 2011;**44**(2):203-215
- [11] Sprecher H. Metabolism of highly unsaturated n-3 and n-6 fatty acids. *Biochimica et Biophysica Acta*. Jul. 2000;**1486**(2-3):219-231
- [12] Joffre C et al. Modulation of brain PUFA content in different experimental models of mice. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2016;**114**:1-10
- [13] Kitajka K et al. Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Proceedings of the National Academy of Sciences of the United States of America*. Jul. 2004;**101**(30):10931-10936
- [14] Chen CT, Bazinet RP. beta-oxidation and rapid metabolism, but not uptake regulate brain eicosapentaenoic acid levels. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Jan. 2015;**92**:33-40
- [15] Green JT, Liu Z, Bazinet RP. Brain phospholipid arachidonic acid half-lives are not altered following 15 weeks of N-3 polyunsaturated fatty acid adequate or deprived diet. *Journal of Lipid Research*. Mar. 2010;**51**(3):535-543
- [16] Orsavova J, Misurcova L, Ambrozova JV, Vicha R, Mlcek J. Fatty acids composition of vegetable oils and its contribution to dietary energy intake and dependence of cardiovascular

- mortality on dietary intake of fatty acids. *International Journal of Molecular Sciences*. Jun. 2015;**16**(6):12871-12890
- [17] Lewinska A, Zebrowski J, Duda M, Gorka A, Wnuk M. Fatty acid profile and biological activities of linseed and rapeseed oils. *Molecules*. Dec. 2015;**20**(12):22872-22880
- [18] Meyer BJ, Mann NJ, Lewis JL, Milligan GC, Sinclair AJ, Howe PRC. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. *Lipids*. Apr. 2003;**38**(4):391-398
- [19] Taber L, Chiu CH, Whelan J. Assessment of the arachidonic acid content in foods commonly consumed in the American diet. *Lipids*. Dec. 1998;**33**(12):1151-1157
- [20] Strobel C, Jahreis G, Kuhnt K. Survey of n-3 and n-6 polyunsaturated fatty acids in fish and fish products. *Lipids in Health and Disease*. Oct. 2012;**11**:144
- [21] Burdge G. Alpha-linolenic acid metabolism in men and women: Nutritional and biological implications. *Current Opinion in Clinical Nutrition and Metabolic Care*. Mar. 2004;**7**(2):137-144
- [22] Lucas M, Asselin G, Mérette C, Poulin M-J, Dodin S. Validation of an FFQ for evaluation of EPA and DHA intake. *Public Health Nutrition*. Oct. 2009;**12**(10):1783-1790
- [23] Blanchard H, Pédrone F, Boulier-Monthéan N, Catheline D, Rioux V, Legrand P. Comparative effects of well-balanced diets enriched in α -linolenic or linoleic acids on LC-PUFA metabolism in rat tissues. Prostaglandins, Leukotrienes, and Essential Fatty Acids. May 2013;**88**(5):383-389
- [24] Taha AY et al. Dietary omega-6 fatty acid lowering increases bioavailability of omega-3 polyunsaturated fatty acids in human plasma lipid pools. Prostaglandins, Leukotrienes, and Essential Fatty Acids. May 2014;**90**(5):151-157
- [25] Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomedicine & Pharmacotherapy*. Oct. 2002;**56**(8):365-379
- [26] Igarashi M, Ma K, Chang L, Bell JM, Rapoport SI. Dietary n-3 PUFA deprivation for 15 weeks upregulates elongase and desaturase expression in rat liver but not brain. *Journal of Lipid Research*. Nov. 2007;**48**(11):2463-2470
- [27] Rao JS, Ertley RN, DeMar JC, Rapoport SI, Bazinet RP, Lee H-J. Dietary n-3 PUFA deprivation alters expression of enzymes of the arachidonic and docosahexaenoic acid cascades in rat frontal cortex. *Molecular Psychiatry*. Feb. 2007;**12**(2):151-157
- [28] DeMar JC Jr, Ma K, Bell JM, Rapoport SI. Half-lives of docosahexaenoic acid in rat brain phospholipids are prolonged by 15 weeks of nutritional deprivation of n-3 polyunsaturated fatty acids. *Journal of Neurochemistry*. Dec. 2004;**91**(5):1125-1137
- [29] Salem N, Kuratko CN. A reexamination of krill oil bioavailability studies. *Lipids in Health and Disease*. Aug. 2014;**13**:137
- [30] Yurko-Mauro K, Kralovec J, Bailey-Hall E, Smeberg V, Stark JG, Salem N. Similar eicosapentaenoic acid and docosahexaenoic acid plasma levels achieved with fish oil or krill oil in a randomized double-blind four-week bioavailability study. *Lipids in Health and Disease*. Sep. 2015;**14**:99
- [31] Carrie I, Clement M, de Javel D, Frances H, Bourre JM. Specific phospholipid fatty acid composition

- of brain regions in mice. Effects of n-3 polyunsaturated fatty acid deficiency and phospholipid supplementation. *Journal of Lipid Research*. Mar. 2000;**41**(3):465-472
- [32] Chung WL, Chen JJ, Su HM. Fish oil supplementation of control and (n-3) fatty acid-deficient male rats enhances reference and working memory performance and increases brain regional docosahexaenoic acid levels. *The Journal of Nutrition*. Jun. 2008;**138**(6):1165-1171
- [33] Little SJ, Lynch MA, Manku M, Nicolaou A. Docosahexaenoic acid-induced changes in phospholipids in cortex of young and aged rats: A lipidomic analysis. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Oct. 2007;**77**(3-4):155-162
- [34] McNamara RK, Carlson SE. Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Oct. 2006;**75**(4-5):329-349
- [35] Xiao Y, Huang Y, Chen ZY. Distribution, depletion and recovery of docosahexaenoic acid are region-specific in rat brain. *The British Journal of Nutrition*. Oct. 2005;**94**(4):544-550
- [36] Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Extrauterine fatty acid accretion in infant brain: Implications for fatty acid requirements. *Early Human Development*. Jun. 1980;**4**(2):131-138
- [37] Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: Implications for fatty acid requirements. *Early Human Development*. Jun. 1980;**4**(2):121-129
- [38] Green P, Glozman S, Kamensky B, Yavin E. Developmental changes in rat brain membrane lipids and fatty acids. The preferential prenatal accumulation of docosahexaenoic acid. *Journal of Lipid Research*. May 1999;**40**(5):960-966
- [39] Giedd JN et al. Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*. Oct. 1999;**2**(10):861-863
- [40] Morgane PJ et al. Prenatal malnutrition and development of the brain. *Neuroscience and Biobehavioral Reviews*. Spring 1993;**17**(1):91-128
- [41] Delion S, Chalon S, Hérault J, Guilloteau D, Besnard JC, Durand G. Chronic dietary alpha-linolenic acid deficiency alters dopaminergic and serotonergic neurotransmission in rats. *The Journal of Nutrition*. Dec. 1994;**124**(12):2466-2476
- [42] McNamara RK, Able J, Jandacek R, Rider T, Tso P. Inbred C57BL/6J and DBA/2J mouse strains exhibit constitutive differences in regional brain fatty acid composition. *Lipids*. Jan. 2009;**44**(1):1-8
- [43] Moriguchi T, Loewke J, Garrison M, Catalan JN, Salem N Jr. Reversal of docosahexaenoic acid deficiency in the rat brain, retina, liver, and serum. *Journal of Lipid Research*. Mar. 2001;**42**(3):419-427
- [44] Hamazaki K, Maekawa M, Toyota T, Dean B, Hamazaki T, Yoshikawa T. Fatty acid composition of the postmortem prefrontal cortex of patients with schizophrenia, bipolar disorder, and major depressive disorder. *Psychiatry Research*. Jun. 2015;**227**(2-3):353-359
- [45] Renaud J, Therien HM, Plouffe M, Martinoli MG. Neuroinflammation: Dr Jekyll or Mr Hyde? *Medical Science (Paris)*. Nov. 2015;**31**(11):979-988

- [46] Bourre JM, Pascal G, Durand G, Masson M, Dumont O, Piciotti M. Alterations in the fatty acid composition of rat brain cells (neurons, astrocytes, and oligodendrocytes) and of subcellular fractions (myelin and synaptosomes) induced by a diet devoid of n-3 fatty acids. *Journal of Neurochemistry*. Aug. 1984;**43**(2):342-348
- [47] Cohen SR, Bernsohn J. Incorporation of 1-¹⁴C labeled fatty acids into isolated neuronal soma, astroglia and oligodendroglia from calf brain. *Brain Research*; **60**(2):521-525
- [48] Morand O, Masson M, Baumann N, Bourre JM. Exogenous [1-¹⁴C]lignoceric acid uptake by neurons, astrocytes and myelin, as compared to incorporation of [1-¹⁴C]palmitic and stearic acids. *Neurochemistry International*. 1981;**3**(5):329-334
- [49] Morand O et al. Alteration in fatty acid composition of neurons, astrocytes, oligodendrocytes, myelin and synaptosomes in intrauterine malnutrition in rat. *Annals of Nutrition & Metabolism*. 1982;**26**(2):111-120
- [50] Rey C et al. Maternal n-3 polyunsaturated fatty acid dietary supply modulates microglia lipid content in the offspring. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. 2018;**133**:1-7
- [51] Madore C et al. Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain, Behavior, and Immunity*. Oct. 2014;**41**:22-31
- [52] Chen CT, Liu Z, Ouellet M, Calon F, Bazinet RP. Rapid beta-oxidation of eicosapentaenoic acid in mouse brain: An in situ study. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Feb. 2009;**80**(2-3):157-163
- [53] Calder PC. Immunomodulation by omega-3 fatty acids. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Dec. 2007;**77**(5-6):327-335
- [54] Alashmali SM, Hopperton KE, Bazinet RP. Lowering dietary n-6 polyunsaturated fatty acids: Interaction with brain arachidonic and docosahexaenoic acids. *Current Opinion in Lipidology*. Feb. 2016;**27**(1):54-66
- [55] Connor WE, Neuringer M, Lin DS. Dietary effects on brain fatty acid composition: The reversibility of n-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. *Journal of Lipid Research*. Feb. 1990;**31**(2):237-247
- [56] Larrieu T, Madore C, Joffre C, Layé S. Nutritional n-3 polyunsaturated fatty acids deficiency alters cannabinoid receptor signaling pathway in the brain and associated anxiety-like behavior in mice. *Journal of Physiology and Biochemistry*. Dec. 2012;**68**(4):671-681
- [57] Delpech J-C et al. Dietary n-3 PUFAs deficiency increases vulnerability to inflammation-induced spatial memory impairment. *Neuropsychopharmacology*. Nov. 2015;**40**(12):2774-2787
- [58] Manduca A et al. Amplification of mGlu5-endocannabinoid signaling rescues behavioral and synaptic deficits in a mouse model of adolescent and adult dietary polyunsaturated fatty acid imbalance. *Journal of Neuroscience*; **37**(29):6851-6868
- [59] Broadhurst CL, Wang Y, Crawford MA, Cunnane SC, Parkington JE, Schmidt WF. Brain-specific lipids from marine, lacustrine, or terrestrial food resources: Potential impact on early African *Homo sapiens*. *Comparative Biochemistry and Physiology. Part B, Biochemistry & Molecular Biology*. Apr. 2002;**131**(4):653-673

- [60] Crawford MA et al. Evidence for the unique function of docosahexaenoic acid during the evolution of the modern hominid brain. *Lipids*. 1999;**34**(Suppl):S39-S47
- [61] Rapoport SI, Rao JS, Igarashi M. Brain metabolism of nutritionally essential polyunsaturated fatty acids depends on both the diet and the liver. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Nov. 2007;**77**(5-6):251-261
- [62] Cho HP, Nakamura MT, Clarke SD. Cloning, expression, and nutritional regulation of the mammalian Delta-6 desaturase. *The Journal of Biological Chemistry*. Jan. 1999;**274**(1):471-477
- [63] Wang Y, Botolin D, Christian B, Busik J, Xu J, Jump DB. Tissue-specific, nutritional, and developmental regulation of rat fatty acid elongases. *Journal of Lipid Research*. Apr. 2005;**46**(4):706-715
- [64] de Theije CG et al. Dietary long chain n-3 polyunsaturated fatty acids prevent impaired social behaviour and normalize brain dopamine levels in food allergic mice. *Neuropharmacology*. Mar. 2015;**90**:15-22
- [65] Hiratsuka S, Koizumi K, Ooba T, Yokogoshi H. Effects of dietary docosahexaenoic acid connecting phospholipids on the learning ability and fatty acid composition of the brain. *Journal of Nutritional Science and Vitaminology (Tokyo)*. Aug. 2009;**55**(4):374-380
- [66] Kitson AP et al. Effect of dietary docosahexaenoic acid (DHA) in phospholipids or triglycerides on brain DHA uptake and accretion. *The Journal of Nutritional Biochemistry*. Jul. 2016;**33**:91-102
- [67] Skorve J et al. Fish oil and krill oil differentially modify the liver and brain lipidome when fed to mice. *Lipids in Health and Disease*. Aug. 2015;**14**:88
- [68] Lacombe RJS, Giuliano V, Colombo SM, Arts MT, Bazinet RP. Compound-specific isotope analysis resolves the dietary origin of docosahexaenoic acid in the mouse brain. *Journal of Lipid Research*. Oct. 2017;**58**(10):2071-2081
- [69] Rey C et al. Dietary n-3 long chain PUFA supplementation promotes a pro-resolving oxylipin profile in the brain. *Brain, Behavior, and Immunity*. Feb. 2019;**76**:17-27
- [70] Orr SK et al. Unesterified docosahexaenoic acid is protective in neuroinflammation. *Journal of Neurochemistry*. Nov. 2013;**127**(3):378-393
- [71] Bascoul-Colombo C, Guschina IA, Maskrey BH, Good M, O'Donnell VB, Harwood JL. Dietary DHA supplementation causes selective changes in phospholipids from different brain regions in both wild type mice and the Tg2576 mouse model of Alzheimer's disease. *Biochimica et Biophysica Acta*. Jun. 2016;**1861**(6):524-537
- [72] Labrousse VF et al. Short-term long chain omega3 diet protects from neuroinflammatory processes and memory impairment in aged mice. *PLoS ONE*. 2012;**7**(5):e36861
- [73] Boudrault C, Bazinet RP, Kang JX, Ma DW. Cyclooxygenase-2 and n-6 PUFA are lower and DHA is higher in the cortex of fat-1 mice. *Neurochemistry International*. Mar. 2010;**56**(4):585-589
- [74] Bousquet M et al. Transgenic conversion of omega-6 into omega-3 fatty acids in a mouse model of Parkinson's disease. *Journal of Lipid Research*. Feb. 2011;**52**(2):263-271
- [75] He C, Qu X, Cui L, Wang J, Kang JX. Improved spatial learning

performance of fat-1 mice is associated with enhanced neurogenesis and neuritogenesis by docosahexaenoic acid. *Proceedings of the National Academy of Sciences of the United States of America*. Jul. 2009;**106**(27):11370-11375

[76] Orr SK, Tong JY, Kang JX, Ma DW, Bazinet RP. The fat-1 mouse has brain docosahexaenoic acid levels achievable through fish oil feeding. *Neurochemical Research*. May 2010;**35**(5):811-819

[77] Delpech J-C et al. Transgenic increase in n-3/n-6 fatty acid ratio protects against cognitive deficits induced by an immune challenge through decrease of neuroinflammation. *Neuropsychopharmacology*. Feb. 2015;**40**(3):525-536

[78] Bowen RA, Clandinin MT. Maternal dietary 22:6n-3 is more effective than 18n:3n-3 in increasing the 22:6n-3 content in phospholipids of glial cells from neonatal rat brain. *The British Journal of Nutrition*. May 2005;**93**(5):601-611

[79] Destailats F et al. Differential effect of maternal diet supplementation with alpha-linolenic acid or n-3 long-chain polyunsaturated fatty acids on glial cell phosphatidylethanolamine and phosphatidylserine fatty acid profile in neonate rat brains. *Nutrition & Metabolism (London)*. Jan. 2010;**7**:2

[80] Layé S. Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. Jun. 2010;**82**(4-6):295-303

[81] Calder PC. Dietary modification of inflammation with lipids. *The Proceedings of the Nutrition Society*. Aug. 2002;**61**(3):345-358

[82] Sperling RI, Benincaso AI, Knoell CT, Larkin JK, Austen KF, Robinson DR. Dietary omega-3 polyunsaturated fatty acids inhibit

phosphoinositide formation and chemotaxis in neutrophils. *The Journal of Clinical Investigation*. Feb. 1993;**91**(2):651-660

[83] P. Needleman, A. Raz, M. S. Minkes, J. A. Ferrendelli, and H. Sprecher Triene prostaglandins: Prostacyclin and thromboxane biosynthesis and unique biological properties. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 76, no. 2, pp. 944-948, Feb. 1979

[84] Obata T, Nagakura T, Masaki T, Maekawa K, Yamashita K. Eicosapentaenoic acid inhibits prostaglandin D2 generation by inhibiting cyclo-oxygenase-2 in cultured human mast cells. *Clinical and Experimental Allergy*. 1999;**29**(8):1129-1135

[85] Calder PC. n-3 fatty acids, inflammation and immunity: New mechanisms to explain old actions. *The Proceedings of the Nutrition Society*. Aug. 2013;**72**(3):326-336

[86] Headland SE, Norling LV. The resolution of inflammation: Principles and challenges. *Seminars in Immunology*. May 2015;**27**(3):149-160

[87] Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: Agonists of resolution. *Current Opinion in Pharmacology*. Aug. 2013;**13**(4):632-640

[88] Serhan CN et al. Resolvins: A family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *The Journal of Experimental Medicine*. Oct. 2002;**196**(8):1025-1037

[89] Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: Dual anti-inflammatory and pro-resolution lipid mediators. *Nature Reviews. Immunology*. May 2008;**8**(5):349-361

- [90] Shalini S-M et al. Distribution of Alox15 in the rat brain and its role in prefrontal cortical resolvin D1 formation and spatial working memory. *Molecular Neurobiology*. 2018;**55**(2):1537-1550
- [91] Nadjar A et al. NFkappaB activates in vivo the synthesis of inducible Cox-2 in the brain. *Journal of Cerebral Blood Flow and Metabolism*. Aug. 2005;**25**(8):1047-1059
- [92] Navarro-Mabarak C, Camacho-Carranza R, Espinosa-Aguirre JJ. Cytochrome P450 in the central nervous system as a therapeutic target in neurodegenerative diseases. *Drug Metabolism Reviews*. 2018;**50**(2):95-108
- [93] Czapski GA, Gajkowska B, Strosznajder JB. Systemic administration of lipopolysaccharide induces molecular and morphological alterations in the hippocampus. *Brain Research*. Oct. 2010;**1356**:85-94
- [94] Schwab JM, Chiang N, Arita M, Serhan CN. Resolvin E1 and protectin D1 activate inflammation-resolution programmes. *Nature*. Jun. 2007;**447**(7146):869-874
- [95] Pratico D et al. 12/15-lipoxygenase is increased in Alzheimer's disease: Possible involvement in brain oxidative stress. *The American Journal of Pathology*. May 2004;**164**(5):1655-1662
- [96] Wang X et al. Resolution of inflammation is altered in Alzheimer's disease. *Alzheimer's & Dementia*. Jan. 2015;**11**(1):40-50 e1-2
- [97] Yigitkanli K, Zheng Y, Pekcec A, Lo EH, van Leyen K. Increased 12/15-lipoxygenase leads to widespread brain injury following global cerebral ischemia. *Translational Stroke Research*. Apr. 2017;**8**(2):194-202
- [98] Sun L, Xu YW, Han J, Liang H, Wang N, Cheng Y. 12/15-Lipoxygenase metabolites of arachidonic acid activate PPARgamma: A possible neuroprotective effect in ischemic brain. *Journal of Lipid Research*. Mar. 2015;**56**(3):502-514
- [99] Bystrom J et al. Endogenous epoxygenases are modulators of monocyte/macrophage activity. *PLoS One*. 2011;**6**(10):e26591
- [100] Fleming I. Cytochrome P450-dependent eicosanoid production and crosstalk. *Current Opinion in Lipidology*. Oct. 2011;**22**(5):403-409
- [101] Gilroy DW et al. CYP450-derived oxylipins mediate inflammatory resolution. *Proceedings of the National Academy of Sciences of the United States of America*. Jun. 2016;**113**(23):E3240-E3249
- [102] Nebert DW, Wikvall K, Miller WL. Human cytochromes P450 in health and disease. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. 2013;**368**(1612):20120431
- [103] Levi G, Minghetti L, Aloisi F. Regulation of prostanoid synthesis in microglial cells and effects of prostaglandin E2 on microglial functions. *Biochimie*. Nov. 1998;**80**(11):899-904
- [104] Farooqui AA, Horrocks LA, Farooqui T. Modulation of inflammation in brain: A matter of fat. *Journal of Neurochemistry*. May 2007;**101**(3):577-599
- [105] Meyer RP, Gehlhaus M, Knoth R, Volk B. Expression and function of cytochrome p450 in brain drug metabolism. *Current Drug Metabolism*. May 2007;**8**(4):297-306
- [106] Volk B, Hettmannsperger U, Papp T, Ameliazad Z, Oesch F, Knoth R. Mapping of phenytoin-inducible cytochrome P450 immunoreactivity

in the mouse central nervous system. *Neuroscience*. 1991;**42**(1):215-235

[107] Barden AE, Mas E, Mori TA. n-3 Fatty acid supplementation and proresolving mediators of inflammation. *Current Opinion in Lipidology*. Feb. 2016;**27**(1):26-32

[108] Halade GV, Black LM, Verma MK. Paradigm shift—Metabolic transformation of docosahexaenoic and eicosapentaenoic acids to bioactives exemplify the promise of fatty acid drug discovery. *Biotechnology Advances*. Aug. 2018;**36**(4):935-953

[109] Recchiuti A. Resolvin D1 and its GPCRs in resolution circuits of inflammation. *Prostaglandins & Other Lipid Mediators*. Dec. 2013;**107**:64-76

[110] Sun YP et al. Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. *The Journal of Biological Chemistry*. Mar. 2007;**282**(13):9323-9334

[111] Mulik RS, Bing C, Ladouceur-Wodzak M, Munaweera I, Chopra R, Corbin IR. Localized delivery of low-density lipoprotein docosahexaenoic acid nanoparticles to the rat brain using focused ultrasound. *Biomaterials*. Mar. 2016;**83**:257-268

[112] Sun W et al. Endogenous expression pattern of resolvin D1 in a rat model of self-resolution of lipopolysaccharide-induced acute respiratory distress syndrome and inflammation. *International Immunopharmacology*. Nov. 2014;**23**(1):247-253

[113] Bisicchia E et al. Resolvin D1 halts remote neuroinflammation and improves functional recovery after focal brain damage via ALX/FPR2 receptor-regulated microRNAs. *Molecular Neurobiology*. Aug. 2018;**55**(8):6894-6905

[114] Fredman G, Serhan CN. Specialized proresolving mediator targets for RvE1 and RvD1 in peripheral blood and mechanisms of resolution. *The Biochemical Journal*. Jul. 2011;**437**(2):185-197

[115] Krishnamoorthy S, Recchiuti A, Chiang N, Fredman G, Serhan CN. Resolvin D1 receptor stereoselectivity and regulation of inflammation and proresolving microRNAs. *The American Journal of Pathology*. May 2012;**180**(5):2018-2027

[116] Recchiuti A, Krishnamoorthy S, Fredman G, Chiang N, Serhan CN. MicroRNAs in resolution of acute inflammation: Identification of novel resolvin D1-miRNA circuits. *The FASEB Journal*. Feb. 2011;**25**(2):544-560

[117] Rey C et al. Resolvin D1 and E1 promote resolution of inflammation in microglial cells in vitro. *Brain, Behavior, and Immunity*. Jul. 2016;**55**:249-259

[118] Aursnes M et al. Total synthesis of the lipid mediator PD1n-3 DPA: Configurational assignments and anti-inflammatory and pro-resolving actions. *Journal of Natural Products*. Apr. 2014;**77**(4):910-916

[119] Doyle R, Sadlier DM, Godson C. Pro-resolving lipid mediators: Agents of anti-ageing? *Seminars in Immunology*. 2018;**40**:36-48

[120] Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *The Journal of Biological Chemistry*. 2003;**278**(17):14677-14687

[121] Kuda O. Bioactive metabolites of docosahexaenoic acid. *Biochimie*. May 2017;**136**:12-20

[122] Marcheselli VL et al. Novel docosanoids inhibit brain

ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. *The Journal of Biological Chemistry*. Oct. 2003;**278**(44):43807-43817

[123] Lukiw WJ et al. A role for docosa-hexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *The Journal of Clinical Investigation*. Oct. 2005;**115**(10):2774-2783

[124] Bazan NG et al. Novel aspirin-triggered neuroprotectin D1 attenuates cerebral ischemic injury after experimental stroke. *Experimental Neurology*. Jul. 2012;**236**(1):122-130

[125] Yao C, Zhang J, Chen F, Lin Y. Neuroprotectin D1 attenuates brain damage induced by transient middle cerebral artery occlusion in rats through TRPC6/CREB pathways. *Molecular Medicine Reports*. Aug. 2013;**8**(2):543-550

[126] Serhan CN et al. Maresins: Novel macrophage mediators with potent antiinflammatory and proresolving actions. *The Journal of Experimental Medicine*. Jan. 2009;**206**(1):15-23

[127] Zhu M et al. Pro-resolving lipid mediators improve neuronal survival and increase Abeta42 phagocytosis. *Molecular Neurobiology*. May 2016;**53**(4):2733-2749

[128] Xian W et al. The pro-resolving lipid mediator Maresin 1 protects against cerebral ischemia/reperfusion injury by attenuating the pro-inflammatory response. *Biochemical and Biophysical Research Communications*. Mar. 2016;**472**(1):175-181

[129] Xian W, Li T, Li L, Hu L, Cao J. Maresin 1 attenuates the inflammatory response and mitochondrial damage in mice with cerebral ischemia/reperfusion

in a SIRT1-dependent manner. *Brain Research*. 2019

[130] Francos-Quijorna I et al. Maresin 1 promotes inflammatory resolution, neuroprotection, and functional neurological recovery after spinal cord injury. *The Journal of Neuroscience*. Nov. 2017;**37**(48):11731-11743

[131] Ohira T, Arita M, Omori K, Recchiuti A, Van Dyke TE, Serhan CN. Resolvin E1 receptor activation signals phosphorylation and phagocytosis. *The Journal of Biological Chemistry*. Jan. 2010;**285**(5):3451-3461

[132] Isobe Y et al. Identification and structure determination of novel anti-inflammatory mediator resolvin E3, 17,18-dihydroxyeicosapentaenoic acid. *The Journal of Biological Chemistry*. Mar. 2012;**287**(13):10525-10534

[133] Chen CT, Liu Z, Bazinet RP. Rapid de-esterification and loss of eicosapentaenoic acid from rat brain phospholipids: An intracerebroventricular study. *Journal of Neurochemistry*. Feb. 2011;**116**(3):363-373

[134] Siegert E, Paul F, Rothe M, Weylandt KH. The effect of omega-3 fatty acids on central nervous system remyelination in fat-1 mice. *BMC Neuroscience*. 2017;**18**(1):19

[135] Krishnamoorthy S et al. Resolvin D1 binds human phagocytes with evidence for proresolving receptors. *Proceedings of the National Academy of Sciences of the United States of America*. Jan. 2010;**107**(4):1660-1665

[136] Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, Serhan CN. Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. *Journal of Immunology*. Mar. 2007;**178**(6):3912-3917

- [137] Ho CF-Y et al. Localisation of formyl-peptide receptor 2 in the rat central nervous system and its role in axonal and dendritic outgrowth. *Neurochemical Research*. Aug. 2018;**43**(8):1587-1598
- [138] Guo X et al. Chronic mild restraint stress rats decreased CMKLR1 expression in distinct brain region. *Neuroscience Letters*. Aug. 2012;**524**(1):25-29
- [139] Graham KL et al. Chemokine-like receptor-1 expression by central nervous system-infiltrating leukocytes and involvement in a model of autoimmune demyelinating disease. *Journal of Immunology*. 2009;**183**(10):6717-6723
- [140] Xu ZZ et al. Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. *Nature Medicine*. May 2010;**16**(5):592-597, 1p following 597
- [141] Qu L, Caterina MJ. Accelerating the reversal of inflammatory pain with NPD1 and its receptor GPR37. *The Journal of Clinical Investigation*. Aug. 2018;**128**(8):3246-3249
- [142] Colas RA, Shinohara M, Dalli J, Chiang N, Serhan CN. Identification and signature profiles for pro-resolving and inflammatory lipid mediators in human tissue. *American Journal of Physiology-Cell Physiology*. Jul. 2014;**307**(1):C39-C54
- [143] Serhan CN, Chiang N, Dalli J. New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. *Molecular Aspects of Medicine*. Dec. 2018;**64**:1-17
- [144] Famenini S et al. Increased intermediate M1-M2 macrophage polarization and improved cognition in mild cognitive impairment patients on omega-3 supplementation. *The FASEB Journal*. Jan. 2017;**31**(1):148-160
- [145] Mizwicki MT et al. 1 α ,25-dihydroxyvitamin D3 and resolvin D1 retune the balance between amyloid-beta phagocytosis and inflammation in Alzheimer's disease patients. *Journal of Alzheimer's Disease*. 2013;**34**(1):155-170
- [146] Uno H et al. Immunonutrition suppresses acute inflammatory responses through modulation of resolvin E1 in patients undergoing major hepatobiliary resection. *Surgery*. 2016;**160**(1):228-236
- [147] Hiram R et al. Resolvin E1 normalizes contractility, Ca²⁺ sensitivity and smooth muscle cell migration rate in TNF- α - and IL-6-pretreated human pulmonary arteries. *American Journal of Physiology. Lung Cellular and Molecular Physiology*. Oct. 2015;**309**(8):L776-L788
- [148] Gyurko R, Van Dyke TE. The role of polyunsaturated ω -3 fatty acid eicosapentaenoic acid-derived resolvin E1 (RvE1) in bone preservation. *Critical Reviews in Immunology*. 2014;**34**(4):347-357
- [149] Abdelmoaty S et al. Spinal actions of lipoxin A4 and 17(R)-resolvin D1 attenuate inflammation-induced mechanical hypersensitivity and spinal TNF release. *PLoS One*. 2013;**8**(9):e75543
- [150] Rossi S et al. Protection from endotoxic uveitis by intravitreal resolvin D1: Involvement of lymphocytes, miRNAs, ubiquitin-proteasome, and M1/M2 macrophages. *Mediators of Inflammation*. 2015;**2015**:149381
- [151] Titos E et al. Resolvin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macrophage polarization toward an M2-like phenotype. *Journal of Immunology*. Nov. 2011;**187**(10):5408-5418

- [152] Li L et al. Resolvin D1 promotes the interleukin-4-induced alternative activation in BV-2 microglial cells. *Journal of Neuroinflammation*. 2014;**11**:72
- [153] Kantarci A et al. Combined administration of resolvin E1 and lipoxin A4 resolves inflammation in a murine model of Alzheimer's disease. *Experimental Neurology*. 2018;**300**:111-120
- [154] Harrison JL et al. Resolvins AT-D1 and E1 differentially impact functional outcome, post-traumatic sleep, and microglial activation following diffuse brain injury in the mouse. *Brain, Behavior, and Immunity*. Jul. 2015;**47**:131-140
- [155] Xu MX et al. Resolvin D1, an endogenous lipid mediator for inactivation of inflammation-related signaling pathways in microglial cells, prevents lipopolysaccharide-induced inflammatory responses. *CNS Neuroscience & Therapeutics*. Apr. 2013;**19**(4):235-243
- [156] Terrando N et al. Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. *The FASEB Journal*. Sep. 2013;**27**(9):3564-3571
- [157] Luo C et al. Enriched endogenous omega-3 fatty acids in mice protect against global ischemia injury. *Journal of Lipid Research*. Jul. 2014;**55**(7):1288-1297
- [158] Furuyashiki T, Akiyama S, Kitaoka S. Roles of multiple lipid mediators in stress and depression. *International Immunology*. 2019
- [159] Deyama S et al. Resolvin D1 and D2 reverse lipopolysaccharide-induced depression-like behaviors through the mTORC1 signaling pathway. *The International Journal of Neuropsychopharmacology*. Jul. 2017;**20**(7):575-584
- [160] Deyama S et al. Resolvin E1/E2 ameliorate lipopolysaccharide-induced depression-like behaviors via ChemR23. *Psychopharmacology*. 2018;**235**(1):329-336
- [161] Deyama S, Shimoda K, Ikeda H, Fukuda H, Shuto S, Minami M. Resolvin E3 attenuates lipopolysaccharide-induced depression-like behavior in mice. *Journal of Pharmacological Sciences*. Sep. 2018;**138**(1):86-88
- [162] Klein CP, Sperotto ND, Maciel IS, Leite CE, Souza AH, Campos MM. Effects of D-series resolvins on behavioral and neurochemical changes in a fibromyalgia-like model in mice. *Neuropharmacology*. Nov. 2014;**86**:57-66
- [163] Gilbert K, Bernier J, Godbout R, Rousseau G. Resolvin D1, a metabolite of omega-3 polyunsaturated fatty acid, decreases post-myocardial infarct depression. *Marine Drugs*. Nov. 2014;**12**(11):5396-5407
- [164] Ishikawa Y et al. Rapid and sustained antidepressant effects of resolvin D1 and D2 in a chronic unpredictable stress model. *Behavioural Brain Research*. Aug. 2017;**332**:233-236
- [165] Zhu M, Wang X, Schultzberg M, Hjorth E. Differential regulation of resolution in inflammation induced by amyloid- β 42 and lipopolysaccharides in human microglia. *Journal of Alzheimer's Disease*. 2015;**43**(4):1237-1250
- [166] Tian Y, Zhang Y, Zhang R, Qiao S, Fan J. Resolvin D2 recovers neural injury by suppressing inflammatory mediators expression in lipopolysaccharide-induced Parkinson's disease rat model. *Biochemical and Biophysical Research Communications*. May 2015;**460**(3):799-805
- [167] Shevalye H et al. Effect of enriching the diet with menhaden oil or daily treatment with resolvin D1 on

neuropathy in a mouse model of type 2 diabetes. *Journal of Neurophysiology*. Jul. 2015;**114**(1):199-208

[168] Hashimoto M et al. n-3 fatty acids effectively improve the reference memory-related learning ability associated with increased brain docosahexaenoic acid-derived docosanoids in aged rats. *Biochimica et Biophysica Acta*. Feb. 2015;**1851**(2):203-209

[169] Taha AY et al. Regulation of rat plasma and cerebral cortex oxylipin concentrations with increasing levels of dietary linoleic acid. *Prostaglandins, Leukotrienes & Essential Fatty Acids*. 2016

[170] Ostermann AI et al. A diet rich in omega-3 fatty acids enhances expression of soluble epoxide hydrolase in murine brain. *Prostaglandins & Other Lipid Mediators*. Nov. 2017;**133**:79-87

[171] Farias SE, Basselin M, Chang L, Heidenreich KA, Rapoport SI, Murphy RC. Formation of eicosanoids, E2/D2 isoprostanes, and docosanoids following decapitation-induced ischemia, measured in high-energy-microwaved rat brain. *Journal of Lipid Research*. Sep. 2008;**49**(9):1990-2000

[172] Yang G, Pan F, Gan WB. Stably maintained dendritic spines are associated with lifelong memories. *Nature*. Dec. 2009;**462**(7275):920-924

[173] Balvers MG et al. Fish oil and inflammatory status alter the n-3 to n-6 balance of the endocannabinoid and oxylipin metabolomes in mouse plasma and tissues. *Metabolomics*. Dec. 2012;**8**(6):1130-1147

[174] Willenberg I, Rund K, Rong S, Shushakova N, Gueler F, Schebb NH. Characterization of changes in plasma and tissue oxylipin levels in LPS and CLP induced murine sepsis. *Inflammation Research*. Feb. 2016;**65**(2):133-142

[175] Rosenberger TA et al. Rat brain arachidonic acid metabolism is increased by a 6-day intracerebral ventricular infusion of bacterial lipopolysaccharide. *Journal of Neurochemistry*. Mar. 2004;**88**(5):1168-1178

[176] Taha AY et al. Dietary linoleic acid lowering reduces lipopolysaccharide-induced increase in brain arachidonic acid metabolism. *Molecular Neurobiology*. Aug. 2017;**54**(6):4303-4315

[177] Dieter P, Scheibe R, Kamionka S, Kolada A. LPS-induced synthesis and release of PGE2 in liver macrophages: Regulation by CPLA2, COX-1, COX-2, and PGE2 synthase. *Advances in Experimental Medicine and Biology*. 2002;**507**:457-462

[178] Le Faouder P et al. LC-MS/MS method for rapid and concomitant quantification of pro-inflammatory and pro-resolving polyunsaturated fatty acid metabolites. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences*. Aug. 2013;**932**:123-133

[179] Slepko N, Minghetti L, Polazzi E, Nicolini A, Levi G. Reorientation of prostanoid production accompanies 'activation' of adult microglial cells in culture. *Journal of Neuroscience Research*. Aug. 1997;**49**(3):292-300

[180] Wang C, Wang M, Zhou Y, Dupree JL, Han X. Alterations in mouse brain lipidome after disruption of CST gene: A lipidomics study. *Molecular Neurobiology*. Aug. 2014;**50**(1):88-96

[181] Jung YS et al. Probulcol inhibits LPS-induced microglia activation and ameliorates brain ischemic injury in normal and hyperlipidemic mice. *Acta Pharmacologica Sinica*. Aug. 2016;**37**(8):1031-1044

[182] Kim HW, Rao JS, Rapoport SI, Igarashi M. Dietary n-6 PUFA deprivation downregulates arachidonate but upregulates docosahexaenoate metabolizing enzymes in rat brain. *Biochimica et Biophysica Acta*. Feb. 2011;**1811**(2):111-117

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